

REMARKS/ARGUMENTS

The following remarks are responsive to the points raised by the Office Action dated February 6, 2008. In view of the following remarks, reconsideration is respectfully requested.

The Pending Claims

Claims 1-40 are pending, of which claims 23-40 are currently under examination, and claims 1-22 are withdrawn.

Incorporation by Reference

The specification and claims were amended to include the amino acid sequences of MART-1 and gp100: 209-217 (210M) peptides, which sequences are incorporated into the specification of the instant application by reference to Kawakami et al., *Proc. Natl. Acad. Sci. U.S.A.* 91: 3515-3519 (1994) and Dudley et al., *J. Immunotherapy* 24: 363-373 (2001), respectively.

According to the Office Action, the amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application.

Submitted herewith is a declaration signed by the practitioner representing the Applicants, Jeremy Jay, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. Accordingly, the objection raised by the Office Action to these amendments has been obviated.

Sufficiency of Declarations under 37 CFR. § 1.131

According to the Office Action, the declaration under 37 CFR § 1.131 of Mark E. Dudley is insufficient on two grounds: 1) because it is not signed by all inventors and 2) because the declaration fails to establish possession of the whole scope of the invention (such as new limitations added into the amended claims) in the sense that the claim as a whole reads on it.

As to the first ground, submitted herewith is a new declaration under 37 CFR § 1.131 signed by all three inventors of the instant patent application, Steven A. Rosenberg, John R. Wunderlich, and Mark E. Dudley.

With respect to the second ground, Rule 1.131 merely requires that the Applicants show possession of the *basic inventive concept* in order to show that they conceived of and reduced to practice the claimed invention prior to July 2, 2001. The new Rule 1.131 declaration submitted herewith evidences that the Applicants had possession of the claimed inventive concept, *i.e.*, the administration of non-myeloablative lymphodepleting chemotherapy followed by adoptive transfer of autologous T cells to melanoma patients. The new Declaration also includes further details of the claimed invention.

Accordingly, it is respectfully submitted that the declaration submitted herewith meets the requirements of Rule 1.131 and evidences that the Applicants conceived of and reduced to practice the claimed invention prior to July 2, 2001.

Rejections under 35 U.S.C. § 103

Claims 23-40 were rejected under 35 U.S.C. § 103 as unpatentable over Dudley et al., *J. Immunother.* 25: 243-251 (2002) (hereinafter, "Dudley 2002") or WO '03/004625 (hereinafter, "WO '625") each in view of Seiter et al., *J. Immunother.* 25: 252-263 (2002) (hereinafter, "Seiter") and Riddell et al., *J. Immunol. Method* 128: 189-201 (1990) (hereinafter, "Riddell").

Claims 23-35, 37 and 38 were rejected under § 103 as unpatentable over Dudley et al., *J. Immunotherapy* 24: 363-373 (2001) (hereinafter, "Dudley 2001") or WO '97/05239 (hereinafter, "WO '239") in view of U.S. Patent No. 6,447,767 to Slavin et al. (hereinafter, "Slavin") and Riddell.

Claims 36, 39, and 40 were rejected under § 103 as unpatentable over Dudley 2001 or WO '239 in view of Slavin and Riddell, as applied to claims 23-35, 37 and 38 above, and further in view of Seiter.

Each of these rejections is separately and respectfully traversed.

*Discussion of the Obviousness Rejections**A. Dudley 2002 or WO '625 each in view of Seiter and Riddell*

As explained in the previous response filed November 19, 2007, the publication date of Dudley 2002 is May-June 2002. While the exact publication date has not been established, it will be assumed, *arguendo*, that Dudley 2002 published as early as May 1, 2002. As supported by the Declaration under 37 C.F.R. Section 131 of Mark E. Dudley, submitted with the November 19, 2007 response, and the Declarations under 37 C.F.R. Section 131 of Steven Rosenberg and John Wunderlich, submitted herewith, the invention was conceived of and reduced to practice before July 2, 2001. Therefore, even if Dudley 2002 published on May 1, 2002, the invention was conceived of and reduced to practice before the publication of Dudley 2002. Accordingly, Dudley 2002 is not prior art to the instant application.

As additionally explained in the previous response filed November 19, 2007, the WO '625 application published on January 16, 2003, indicating a priority date of July 2, 2001. As supported by the Declaration under 37 C.F.R. Section 131 of Mark E. Dudley, submitted with the November 19, 2007 response, and the Declarations under 37 C.F.R. Section 131 of Steven Rosenberg and John Wunderlich, submitted herewith, the invention was conceived of and reduced to practice before July 2, 2001. Accordingly, WO '625 is not prior art to the instant application.

Also as explained in the previous response filed November 19, 2007, the publication date of Seiter is May-June 2002. While the exact publication date has not been established, it will be assumed, *arguendo*, that Seiter published as early as May 1, 2002. As the invention was conceived of and reduced to practice before July 2, 2001 (as discussed above), which is before the publication date of Seiter, Seiter is not prior art to the instant application.

In view of the foregoing, none of Dudley 2002, WO '625, and Seiter are prior art to the instant application, such that the obviousness rejection in view of these references cannot stand. Applicants therefore request that the obviousness rejection is withdrawn.

Even assuming, *arguendo*, that Dudley 2002, WO '625, and Seiter are prior art that could be applied to the instant claims, the rejection of the claims based on Dudley 2002 or WO '625 each in view of Seiter and Riddell cannot be maintained because Riddell fails to

teach administering to cancer patients autologous T-cells that have been stimulated *in vitro* with an antigen of the cancer followed by *one* cycle of rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody, and IL-2. In fact, Riddell teaches away from using one cycle of rapid expansion because Riddell teaches that successful adoptive immunotherapy requires large numbers of T-cells, which are obtained through the use of *repetitive* stimulation with anti-CD3:

Moreover, the application of approaches to adoptive immunotherapy developed in animal models to the treatment of human viral or malignant diseases requires the generation of large numbers of viral or tumor specific T-cells for *in vivo* administration. Therefore, the use of *repetitive* stimulation with CD3 or anti-CD3 and anti-CD28 was explored as a means of expanding T cell clones to large numbers.

(Riddell, pages 194-195, carryover paragraph, emphasis added). Riddell proceeds to conclude that “this culture method had the potential to promote growth of antigen-specific T-cell clones in long-term culture to cell numbers sufficient for clinical use in adoptive immunotherapy, without the need for specific Ag stimulation during cell growth” (Riddell, page 195, first full paragraph, right column). In view of Riddell, a single rapid expansion would not be expected to generate large enough numbers of T cells for successful adoptive immunotherapy. Therefore, the obviousness rejection based on Riddell cannot be maintained.

Moreover, one of ordinary skill in the art would not have expected a single round of rapid expansion to produce high enough numbers of T cells to be effective in adoptive immunotherapy. As shown in Riddell and Dudley 2002, each of which teach the use of multiple rounds of rapid expansion, one of ordinary skill in the art would have believed that multiple rounds of rapid expansion were necessary for successful adoptive immunotherapy and that a single round of rapid expansion would not have been sufficient to generate enough T cells for effective adoptive immunotherapy.

Surprisingly and unexpectedly, as shown in Example 1 of the instant patent application, six out of thirteen patients who were administered autologous T-cells that were selected for recognition of a tumor antigen, followed by one cycle of rapid expansion, had objective clinical responses to the treatment and four others demonstrated mixed responses

with significant shrinkage of one or more metastatic deposits. Objective tumor regression was seen in the lung, liver, lymph nodes, and intraperitoneal masses, and at cutaneous and subcutaneous sites. Five patients, all with evidence of concomitant cancer regression, demonstrated signs of autoimmune melanocyte destruction. Because the presently claimed method provides unexpectedly successful results with one cycle of rapid expansion, contrary to the commonly accepted teaching shown in Dudley 2002 and Riddell to use multiple rounds of rapid expansion, the obviousness rejections based on Dudley 2002 and Riddell cannot be maintained.

B. Dudley 2001 or WO '239 in view of Slavin and Riddell

The obviousness rejection based on Dudley 2001 or WO '239 in view of Slavin and Riddell cannot be maintained because none of these references teach or suggest administering non-myeloablative lymphodepleting chemotherapy prior to the administration of autologous T-cells, as claimed in independent claim 23.

Dudley 2001 merely states that "additional adjuvant treatments for the patient (e.g., ablation of endogenous lymphocytes) might improve lymphocyte survival and treatment efficacy" (page 372, right column). Dudley 2001, however, fails to explicitly teach a treatment protocol comprising administering *non-myeloablative* lymphodepleting chemotherapy *prior* to the administration of autologous T-cells, as claimed in independent claim 23.

WO '239 contains no mention or suggestion of any administration of non-myeloablative lymphodepleting chemotherapy at any time during the treatment protocol.

According to the Office Action, Slavin teaches a method of treating cancer patients comprising administering to the patient non-myeloablative treatment, including administering cyclophosphamide and fludarabine prior to the administration of T-cells.

Slavin, however, does not teach administering non-myeloablative lymphodepleting chemotherapy prior to the administration of T-cells. On the contrary, Slavin teaches administering non-myeloablative lymphodepleting therapy prior to the administration of hematopoietic *stem* cells (Slavin, e.g., col. 7, line 64 to col. 8, line 9). Stem cells are unspecialized cells that later give rise to specialized cells. As unspecialized cells, stem cells

are quite far removed from T-cells in general, which are specialized, and even farther removed from “autologous T-cells that have been previously isolated and selected for highly avid recognition of an antigen of the cancer,” as claimed in claim 23. Slavin further teaches that it is crucial to remove any T-cells in the hematopoietic stem cell preparation or to use lifespan-limited lymphocytes whenever the donor-reactive host T cells are effectively depleted in order to prevent graft versus host disease (Slavin, col. 12, lines 15-20). Thus, the teachings of Slavin, as a whole, are *not* to administer T-cells following non-myeloablative lymphodepleting therapy, in direct contrast to the claimed method. Accordingly, Slavin does not cure the deficiencies of Dudley 2001 and WO ‘239. Therefore, the obviousness rejection in view of Slavin cannot be maintained.

Additionally, the obviousness rejection in view of Riddell cannot be maintained for the reasons set forth above.

Like Riddell, Dudley 2001 also teaches using multiple rounds of rapid expansion to generate large numbers of T cells for adoptive immunotherapy. For the reasons explained above, because the presently claimed method provided unexpectedly successful results with one cycle of rapid expansion, contrary to the commonly accepted teaching as shown in Dudley 2001 and Riddell to use multiple rounds of rapid expansion, the obviousness rejections based on Dudley 2001 and Riddell cannot be maintained.

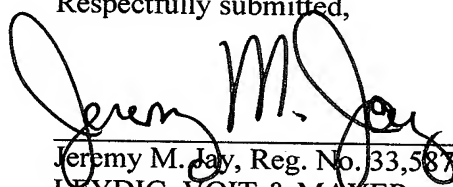
C. Dudley 2001 or WO ‘239 in view of Slavin and Riddell and further in view of Seiter

The rejection is traversed, because, as discussed above, Seiter is not prior art to the instant application. Also, as discussed herein, the ‘239 application does not teach or suggest a treatment protocol comprising administering non-myeloablative lymphodepleting chemotherapy. In view of the foregoing, the rejection cannot stand. Applicants therefore request that the rejection be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Jeremy M. Jay", is written over a horizontal line.

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